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AMENDMENTS TO THE SPECIFICATION:

Please amend the specification as follows:

Abstract, line 2, delete, "comprising":

A novel formulation is provided that serves to specifically inhibit the COX-2 mediated inflammatory response in animals. The formulation comprises ~~comprising~~ an effective amount of component I selected from the group consisting of alpha acids and beta acids and an effective amount of at least one component II selected from the group consisting of alpha acids, beta acids, essential oils, fats and waxes, with the proviso that component I and II are not the same compound. The composition provides specific inhibition of cyclooxygenase-2 with little or no effect on cyclooxygenase-1.

Paragraph [0001], line 3, amend, "methods":

[0001] The present invention relates generally to a composition comprising a complex mixture of active ingredients exhibiting selective inhibition of inducible cyclooxygenase-2 (COX-2) and methods for selective inhibition of COX-2 mediated synthesis of prostaglandins.

Paragraph [0003], line 6, amend, "arachidonic acid (AA)":

[0003] inflammatory diseases affect more than fifty million Americans. As a result of basic research in molecular and cellular immunology over the last ten to fifteen years, approaches to diagnosing, treating and preventing these immunologically-based diseases has been dramatically altered. One example of this is the discovery of an inducible form of the cyclooxygenase enzyme. Constitutive cyclooxygenase (COX), first purified in 1976 and cloned in 1988, functions in the synthesis of prostaglandins (PGs) from arachidonic acid (AA). Three years after its purification, an inducible enzyme with COX activity was identified and given the name COX-2, while constitutive COX was termed COX-1.

Paragraph [0008], lines 4 and 6, amend, "C[[.]]":

[0008] Hop extraction in one form or another goes back over 150 years to the early nineteenth century when extraction in water and ethanol was first attempted. Even today an ethanol extract is available in Europe, but by far the predominant extracts are organic solvent extracts (hexane) and CO_2 extracts (supercritical and liquid). CO_2 (typically at 60 bars pressure and 5 to 10° C[[.]]) is in a liquid state and is a relatively mild, non-polar solvent highly specific for hop soft resins and oils. Beyond the critical point, typically at 300 bars pressure and 60° C[[.]], CO_2 has the properties of both a gas and a liquid and is a much stronger solvent. The composition of the various extracts is compared in Table 1.

Paragraph [0022], line 6, amend, "α-acids, β-acids and essential oils":

[0022] The present invention provides a composition comprising an effective amount of component I selected from the group consisting of alpha acids and beta acids and an effective amount of at least one component II selected from the group consisting of alpha acids, beta acids, essential oils, fats and waxes, with the proviso that component I and II are not the same compound. Preferably, the composition comprises two or more active ingredients selected from the group consisting of α-acids, β-acids and essential oils. The active ingredients of the present invention are preferably made from hops extract. The composition functions synergistically to inhibit the activity of inducible COX-2 with little or no effect on COX-1.

Paragraph [0025], line 5, amend, "α-acids, β-acids and essential oils":

[0025] The present invention further provides a method of dietary supplementation and a method of treating inflammation or inflammation-based diseases in an animal which comprises providing to the animal suffering symptoms of inflammation, including pain and swelling, the composition of the present invention containing two or more active ingredients selected from the group consisting of α-acids, β-acids and essential oils and continuing to administer such a dietary supplementation of the composition until said symptoms are eliminated or reduced.

Paragraph [0026], line 3, add, "that":

[0026] Before the present composition and methods of making and using thereof are disclosed and described, it is to be understood that this invention is not limited to the particular configurations, as process steps, and that materials may vary somewhat. It is also intended to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

Paragraph [0028], line 8, amend, "[[Hops]] hops"; line 9, amend, "~~a-acids~~ α-acids":

[0028] The present invention provides a composition having a selective inhibitory effect on the activity of COX-2, said composition comprising an effective amount of component I selected from the group consisting of alpha acids and beta acids and an effective amount of at least one component II selected from the group consisting of alpha acids, beta acids, essential oils, fats and waxes, with the proviso that component I and II are not the same compound. More particularly, the composition comprises two or more active ingredients selected from the groups consisting of α-acids, β-acids and essential oils. Preferably, the active ingredients of the present invention are made from [[Hops]] hops extract. Preferably, composition comprising an 30 to 60 weight percent of ~~a-acids~~ α-acids, 15 to 45 weight percent of β-acids and 3 to 6 weight percent of essential oils. The composition optionally comprises 2 to 8 weight percent of fats and waxes. Preferably, the α-acids, β-acids, essential oils, fats or waxes are from a hop extract, which is preferably prepared by CO_2 extraction. The composition provided by the present invention can be formulated as a dietary supplement or therapeutic composition. The composition functions to inhibit the inducibility and/or activity of COX-2 with little or no effect on COX-1.

Paragraph [0033], line 2, remove, "[[the]]":

[0033] As used herein, the term "CO_2 extract" refers to the solid material resulting from exposing a hops plant product to a liquid or supercritical CO_2 preparation followed by [[the]] removing the CO_2.

Paragraph [0039], line 3, amend, "α-acids, β-acids and essential oils":

[0039] Therefore, one preferred embodiment of the present invention is a composition comprising a combination of an effective amount of two or more active ingredients selected from the group consisting of α-acids, β-acids and essential oils. The composition of the present invention functions to specifically inhibit the inducibility and/or activity of COX-2 while showing little or no effect on COX-1. Therefore, the composition of the present invention essentially eliminates the inflammatory response, including pain and swelling, rapidly without introducing any harmful side effects.

Paragraph [0049], line 3, amend, "Therefore, it is", and, "[[CO2]] CO_2":

[0049] This example illustrates a superior COX-2 selectivity of the CO_2 hops extract of the present invention compared to the pure compound humulone described in the prior art. Therefore, it is to be inferred that the effectiveness of the [[CO2]] CO_2 hops extract of the present invention would be superior to the pure compound humulone described in the prior art.

Paragraph [0051], line 11, amend, "C[[.]]":

[0051] Equipment--balancer, analytical, Ohaus Explorer (Ohaus Model #EO1140, Switzerland), biosafety cabinet (Forma Model #F1214, Marietta, Ohio), pipettor, 100 to 1000 µL (VWR Catalog #4000-208, Rochester, N.Y.), cell hand tally counter (VWR Catalog #23609-102, Rochester, N.Y.), CO_2 incubator (Forma Model #F3210, Marietta, Ohio), hemacytometer (Hausser Model #1492, Horsham, Pa.), microscope, inverted (Leica Model #DM IL, Wetzlar, Germany), multichannel pipettor, 12-Channel (VWR Catalog #53501-662, Rochester, N.Y.), Pipet Aid (VWR Catalog #53498-103, Rochester, N.Y.), Pipettor, 0.5 to 10 L (VWR Catalog #4000-200, Rochester, N.Y.), pipettor, 100 to 1000 µL (VWR Catalog #4000-208, Rochester, N.Y.), pipettor, 2 to 20 µL (VWR Catalog #4000-202, Rochester, N.Y.), pipettor, 20 to 200 µL (VWR Catalog #4000-204, Rochester, N.Y.), PLRELAB Plus Water Polishing System (U.S. Filter, Lowell, Mass.), refrigerator, 4° C[[.]] (Forma Model #F3775, Marietta, Ohio), vortex mixer (VWR Catalog #33994-306, Rochester, N.Y.), water bath (Shel Lab Model #1203, Cornelius, Oreg.).

Paragraph [0053], line 1, amend, "General Procedure"; line 4, amend, "results" and "37° C":

[0053] General Procedure--RAW 264.7 cells, obtained from ATCC, were grown in DMEM medium and maintained in log phase. The DMEM growth medium was made as follows: 50 mL of heat inactivated FBS and 5 mL of penicillin/streptomycin was added to a 500 mL bottle of DMEM and stored at 4° C. For best results the medium is to be used within three months and warmed to 37° C in water bath before use.

Paragraph [0054], lines 6-8, amend as follows:

[0054] On day one of the experiment, the log phase 264.7 cells were plated at $8x10^4$ cells per well in 0.2 mL growth medium per well in a 96-well tissue culture plate in the morning. At the end of the day 1 (6 to 8 hours post plating), 100 µL of growth medium from each well were removed and replaced with 100 µL fresh medium. A 1.0 mg/mL solution of LPS, which is used to induce the expression of COX-2 in the RAW 264.7 cells, was prepared by dissolving 1.0 mg of LPS in 1 mL DMSO. It was vortexed until it dissolved and was stored at 4° C. ~~Melt~~ It was melted at room temperature or in a 37° C[[.]] water bath before use. ~~Make up a new solution~~ New solutions were prepared every 60 days.

Paragraph [0056], line 5, amend, "of LPS" and "of LPS":

[0056] One-hundred microliters of medium was removed from each well of the cell plates prepared on day one. One-hundred microliter of equilibrated 2.times. final concentration the test compounds was added to cells and incubated for 90 minutes. LPS in DMEM without FBS was prepared by adding 44 µL of the 1 mg/mL DMSO stock to 10 mL of medium. For each well of cells to be stimulated, 20 µL of LPS (final concentration ofLPS is 0.4 µg/mL of LPS) was added and incubated for 24 hours.

Paragraph [0060], lines 3-4 and 13, amend, "C[[.]]"; line 32, amend, "of hops"; line 15, SPLIT TO FORM NEW PARAGRAPH, add, "[0061]" to number the new paragraph:

[0060] Equipment--balancer (2400 g, Acculab VI-2400, VWR Catalog #11237-300, Rochester, N.Y.), balancer, analytical, Ohaus Explorer (Ohaus Model #EO 1140, Switzerland), biosafety cabinet (Forma Model #F1214, Marietta, Ohio), Freezer, -30° C[[.]] (Forma Model #F3797), Freezer, -80° C[[.]] Ultralow (Forma Model #F8516, Marietta, Ohio), heated stirring plate (VWR Catalog #33918-262, Rochester, N.Y.), ice maker (Scotsman Model #AFE400A-1A, Fairfax, S.C.), multichannel pipettor, 12-Channel (VWR Catalog #53501-662, Rochester, N.Y.), Multichannel Pipettor, 8-Channel (VWR Catalog #53501-660, Rochester, N.Y.), orbital shaker platform (Scienceware #F37041-0000, Pequannock, N.J.), pH meter (VWR Catalog #33221-010, Rochester, N.Y.), pipet aid (VWR Catalog #53498-103, Rochester, N.Y.), pipettor, 0.5 to 10 µL (VWR Catalog #4000-200, Rochester, N.Y.), pipettor, 100 to 1000 µL (VWR Catalog #4000-208, Rochester, N.Y.), pipettor, 2 to 20 µL (VWR Catalog #4000-202, Rochester, N.Y.), pipettor, 20 to 200 µL (VWR Catalog #4000-204, Rochester, N.Y.), PURELAB Plus Water Polishing System (U.S. Filter, Lowell, Mass.), refrigerator, 4° C[[.]] (Forma Model #F3775, Marietta, Ohio), vacuum chamber (Sigma Catalog #Z35, 407-4, St. Louis, Mo.), vortex mixer (VWR Catalog #33994-306, Rochester, N.Y.)

[0061] Supplies and Reagents--96-Well, round-bottom plate (Nalge Nunc #267245, Rochester, N.Y.), arachidonic acid (Sigma Catalog #A-3925, St. Louis, Mo.), centrifuge tubes, 15 mL, conical, sterile (VWR Catalog #20171-008, Rochester, N.Y.), COX-1 enzyme (ovine) 40,000 units/mg (Cayman Chemical Catalog #60100, Ann Arbor, Mich.), dimethylsulfoxide (DMSO) (VWR Catalog #5507, Rochester, N.Y.), ethanol 100% (VWR Catalog #MK701908, Rochester, N.Y.), epinephrine (Sigma Catalog #E-4250, St. Louis, Mo.), glutathione (reduced) (Sigma Catalog #G-6529, St. Louis, Mo.), graduated cylinder, 1000 mL (VWR Catalog #24711-364, Rochester, N.Y.), hematin (porcine) (Sigma catalog #H-3281, St. Louis, Mo.), hydrochloric acid (HCl) (VWR Catalog #VW3110-3, Rochester, N.Y.), KimWipes (Kimberly Clark Catalog #34256, Roswell, Ga.), microfuge tubes, 1.7 mL (VWR Catalog #20172-698, Rochester, N.Y.), NaOH (Sigma Catalog #S-5881, St. Louis, Mo.), pipet tips for 0.5 to 10 µL pipettor (VWR Catolog #53509-138, Rochester, N.Y.), pipet tips for 100-1000 µL pipettor (VWR Catolog #53512-294, Rochester, N.Y.), pipet tips for 2-20 µL and 20-200 µL pipettors (VWR Catolog #53512-260, Rochester, N.Y.), prostaglandin E2 (Sigma Catalog #P-5640, St. Louis, Mo.), prostaglandin F2alpha (Sigma Catalog #P-0424, St. Louis, Mo.), stir bar, magnetic (VWR Catalog #58948-193, Rochester, N.Y.), storage bottle, 1000 mL (Corning Catalog #1395-1L, Corning, N.Y.), storage bottle, 100 mL (Corning Catalog #1395-100, Corning, N.Y.), CO_2 extract of hops (Hopunion, Yakima, Wash.), Tris-HCl (Sigma Catalog #T-5941, St. Louis, Mo.), ultra-pure water (Resistance =18 megaOlun-cm deionized water).

Paragraph [0061], lines 1, amend, "~~[0061]~~ [0062]" and "1.0 M":

~~[0061]~~ [0062] General Procedure--Oxygen-free 1.0 M Tris-HCl buffer (pH 8.0) was prepared as follows: In a 1000 mL beaker, 12.11 g Trizma HCl was dissolved into 900 mL ultra-pure water. The beaker was placed on a stir plate with a stir bar. NaOH was added until the pH reached 8.0. The volume was adjusted to a final volume of 1000 mL and stored in a 1000 mL storage bottle.

Paragraph [0062], line 1, amend, "~~[0062]~~ [0063]", line 3, amend, "tightly covered [[tight]]":

~~[0062]~~ [0063] The Tris-HCl buffer was placed into a vacuum chamber with a loose top and the air pump was turned on until the buffer stopped bubbling. The vacuum chamber was turned off and the storage bottle was tightly covered [[tight]]. This step was repeated each time when the oxygen-free Tris-HCl buffer was used.

Paragraph [0063], line 1, amend, "~~[0063]~~ [0064] A":

~~[0063]~~ [0064] A 1 mL cofactor solution was prepared by adding 1.3 mg (-) epinephrine, 0.3 mg reduced glutathione and 1.3 mg hematin to 1 mL oxygen free Tris-HCl buffer. Solutions of the test material were prepared as needed. i.e. 10 mg of aspirin was weighed and dissolved into 1 ml DMSO.

Paragraph [0064], line 1, amend, "~~[0064]~~ [0065]"; lines 6-8, amend "[[µl]] µL"; line 9, amend, "50, 25"; line 10, amend, "(30 µM)":

~~[0064]~~ [0065] Enzyme was dissolved in oxygen free Tris-HCl buffer as follows, i.e. on ice, 6.5 µL of enzyme at 40,000 units/mL was taken and added to 643.5 µL of oxygen free Tris-HCl buffer. This enzyme solution is enough for 60 reactions. The COX-1 enzyme solution was prepared as follows. In a 15 mL centrifuge tube, 10 µL COX-1 enzyme at 40,000 units/mL was added in oxygen free Tris-HCl with 50 µL of the cofactor solution per reaction. The mixture was incubated on ice for 5 minutes (i.e. for 60 reactions add 650 [[µl]] µL enzyme in oxygen free Tris-HCl buffer with 3.25 mL cofactor solution). 60 [[µl]] µL of the enzyme solution was combined with 20 [[µl]] µL of the test solution in each well of a 96 well plate. Final concentrations of the test solutions were 100, 50, 25, 12.5, 6.25 and 3.12 µg/mL. The plates were preincubated on ice for 10 minutes. 20 µL arachidonic acid (30 µM) was added and incubated for 15 minutes at 37° C.

Paragraph [0065], line 1, amend, "~~[0065]~~ [0066]":

~~[0065]~~ [0066] 2 M HCl was prepared by diluting 12.1 N HCl. In a 100 mL storage bottle, 83.5 mL ultra-pure water was added and then 16.5 mL 12.1 N HCl was added. It was stored in a 100 mL storage bottle and placed in the biosafety cabinet (always add acid last). The reaction was terminated by adding 10 µL 2 M HCl. The final solution was used as the supernate for the PGE_2 assay.

Paragraph [0066], line 1, amend, "~~[0066]~~ [0067]":

~~[0066]~~ [0067] Determination of PGE2 Concentration in Medium—

Paragraph [0067], COMBINE WITH THE PARAGRAPH ABOVE, remove, "~~[0067]~~":

~~[0067]~~ The procedure followed was that essentially described by Hamberg, M. and Samuelsson, B. (J. Biol. Chem. 1971. 246, 6713-6721); however a commercial, nonradioactive procedure was employed.

Paragraph [0068], lines 1 and 9, amend, "C[[.]]":

[0068] Equipment--freezer, -30° C[[.]] (Forma Model #F3797), heated stirring plate (VWR Catalog #33918-262, Rochester, N.Y.), multichannel pipettor, 12-Channel (VWR Catalog #53501-662, Rochester, N.Y.), orbital shaker platform (Scienceware #F37041-0000, Pequannock, N.J.), PipetAid (VWR Catalog #53498-103, Rochester, N.Y.), pipettor, 0.5 to 10 µL (VWR Catalog #4000-200, Rochester, N.Y.), pipettor, 100 to 1000 µL (VWR Catalog #4000-208, Rochester, N.Y.), pipettor, 2 to 20 µL (VWR Catalog #4000-202, Rochester, N.Y.), pipettor, 20 to 200 µL (VWR Catalog #4000-204, Rochester, N.Y.), plate reader (Bio-tek Instruments Model #Elx800, Winooski, Vt.), PURELAB Plus Water Polishing System (U.S. Filter, Lowell, Mass.), refrigerator, 4° C[[.]] (Forma Model #F3775, Marietta, Ohio).

Paragraph [0069], line 4, amend, "100 [[ML]] mL (":

[0069] Chemicals, Reagents and Buffers--Prostaglandin E_2 EIA Kit-Monoclonal 480-well (Cayman Chemical Catalog #514010, Ann Arbor, Mich.), centrifuge tube, 50 mL, conical, sterile (VWR Catalog #20171-178, Rochester, N.Y.), Dulbecco's Modification of Eagle's Medium (DMEM) (Mediatech Catalog #10-013-CV, Herndon, Va.), graduated cylinder, 100 [[ML]] mL (VWR Catalog #24711-310, Rochester, N.Y.), KimWipes (Kimberly Clark Catalog #34256, Roswell, Ga.), microfuge tubes, 1.7 mL (VWR Catalog #20172-698, Rochester, N.Y.), penicillin/streptomycin (Mediatech Catalog #30-001-CI, Herndon, Va.), pipet tips for 0.5 to 10 µL pipettor (VWR Catolog #53509-138, Rochester, N.Y.), pipet tips for 100-1000 µL pipettor (VWR Catolog #53512-294, Rochester, N.Y.), pipet tips for 2-20 µL and 20-200 µL pipettors (VWR Catolog #53512-260, Rochester, N.Y.), pipets, 25 mL (Becton Dickinson Catalog #7551, Marietta, Ohio), storage bottle, 100 mL (Corning Catalog #1395-100, Corning, N.Y.), storage bottle, 1000 mL (Corning Catalog #1395-1L, Corning, N.Y.), ultra-pure water (Resistance =18 megaOhm-cm deionized water).

Paragraph [0071], lines 3-4, amend, "[[.]], i.e. [[(For]] for...[[)]]"; lines 2-4, amend, "[[ml]] mL":

[0071] The Wash Buffer was prepared by diluting Wash Buffer Concentrate (vial #5) 1:400 with Ultra-pure water. 0.5 [[ml]] mL/liter of Tween 20 (vial #5a) was then added (using a syringe for accurate measurement)[[.]], i.e. [[(For]] for one liter Wash Buffer add 2.5 [[ml]] mL Wash Buffer Concentrate, 0.5 [[ml]] mL Tween-20, and 997 [[ml]] mL Ultra-pure water.[[)]] The solution was stored in a 1 liter storage bottle at 4° C.

Paragraph [0072], line3-4, amend, "[[µl]] µL" and "C[[.]]":

[0072] The Prostaglandin E_2 standard was reconstituted as follows. A 200 µL pipet tip was equilibrated by repeatedly filling and expelling the tip several times in ethanol. The tip was used to transfer 100 µL of the PGE_2 Standard (vial #3) into a 1.7 mL microfuge tube. 900 [[µl]] µL Ultra-pure water was added to the tube and stored at 4° C[[.]], which was stable for ~6 weeks.

Paragraph [0076], line 2, amend, "(B_0[[,]])":

[0076] The plate was set up as follows: Each plate contained a minimum of two blanks (B), two non-specific binding wells (NSB), two maximum binding wells (B_0[[,]]), and an eight point standard curve run in duplicate (S1-S8). Each sample was assayed at a minimum of two dilutions and each dilution was run in duplicate.

Paragraph [0078], lines 1-2 & 6, amend, "[[µl]] µL"; line 4, amend, "next two":

[0078] Fifty microliters of EIA Buffer and 50 [[µl]] µL DMEM were added into the NSB wells. Fifty [[µl]] µL DMEM was added to the Bo wells. Fifty microliters of solution was taken from tube #8 and added to both the lowest standard wells (S8). Fifty microliters was taken from tube #7 and added to each of the next two wells. Continue this through to tube #1. (Use the same pipet tip for all 8 of the standards. Make sure to equilibrate the tip in each new standard by pipeting up and down in that standard. Using a P200, add 50 [[µl]] µL of each sample at each dilution to the sample wells).

Paragraph [0078], lines 1 & 3, amend, "[[µl]] µL":

[0079] Using the 12 channel pipetor, 50 [[µl]] µL of the Prostaglandin E_2 acetylcholinesterase tracer was added to each well except the Total Activity (TA) and the Blank (B) wells. Using the 12 channel pipetor, 50 [[µl]] µL of the Pro staglandin E_2 monoclonal antibody was added to each well

except the Total Activity (TA), the (NSB), and the Blank (B) wells. The plate was covered with plastic film (item #7) and incubated for 18 hours at 4° C.

Paragraph [0083], COMBINE WITH PARAGRAPH [0082], remove, "[0083]":

~~[0083]~~ The medium inhibitory concentration of the CO_2 hops extract for both COX-2 and COX-1 were assessed using CalcuSyn (BIOSOFT, biosoft.com). This statistical package performs multiple drug dose-effect calculations using the Median Effect methods described by T-C Chou and P. Talaly (Trends Pharmacol. Sci. 4:450-454). Briefly, it correlates the "Dose" and the "Effect" in the simplest possible form: fa/fu =(C/Cm).sup.m, where C is the concentration or dose of the compound and Cm is the median-effective dose signifying the potency. Cm is determined from the x-intercept of the median-effect plot. The fraction affected by the concentration of the test material is fa and the fraction unaffected by the concentration is fu (fu=1-fa). The exponent m is the parameter signifying the sigmoidicity or shape of the dose-effect curve. It is estimated by the slope of the median-effect plot.

Paragraph [0084], line 1, amend, "~~[0084]~~ [0083]":

~~[0084]~~ [0083] The median-effect plot is a plot of x=log(C) vs y=log(fa/fu) and is based on the logarithmic form of Chou's median-effect equation. The goodness of fit for the data to the median-effect equation is represented by the linear correlation coefficient r of the median-effect plot. Usually, the experimental data from enzyme or receptor systems have r>0.96, from tissue culture or enzyme work.

Paragraph [0085], amend, "~~[0085]~~ [0084]", and remove, "[[The]]":

~~[0085]~~ [0084] Results [[The]]

Paragraph [0086], line 1, amend, "~~[0086]~~ [0085] The"; lines 1 & 3, amend, "[[CO2]] CO_2"; line 2, amend, "~~0.0.24~~ 0.24":

~~[0086]~~ [0085] The medium inhibitory concentration of COX-2 inhibition by the [[CO2]] CO_2-extract of hops in the RAW 264.7 cell model was ~~0.0.24~~ 0.24 µg/mL (95% CI=0.16-0.36). The same [[CO2]] CO_2 extract of hops demonstrated a median inhibitory concentration of COX-1 production of PGE2 of 25.5 µg/mL. Thus, a COX-1/COX-2 specificity of 106 is observed. This COX-2 specificity is 2.7-fold greater than the COX-2 specificity demonstrated for pure humulone in the TNFalpha stimulation of MC3T3-E1 cells [Yamamoto, K. 2000. Suppression of cyclooxygenase-2 gene transcription by humulon of bee hop extract studied with reference to glucocorticoid. FEBS Letters 465:103-106]. Such alarge difference in COX-2 specificity between the pure compound and the complex mixture is unexpected and constitutes a novel finding. It is unusual that a complex mixture would contain greater specific biological activity than the most active molecule. The inference is that an underlying synergy among the bioactive molecules, including humulone, is to account for such an effect.